Osmolar and Free Water Clearance During Hemorrhagic Shock in the Dog.* (27873)

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One of the most significant functional alterations of the kidney subjected to prolonged hemorrhagic hypotension is loss of urinary concentrating power. More specifically, osmolar U/P ratios approach unity, and free water clearance, which is negative in the concentrating kidney, becomes zero, with the result that urine is typically isosmotic with plasma.

Because the ability of the kidney to concentrate depends on the development of hyperosmolarity in the region of the papilla (Wirz, *et al.*(1), Gottschalk and Mylle(2)), loss of concentrating power would result from dissipation of the osmotic gradient, stratified from cortex to papilla, with highest concentration in the papilla. Kramer(3) has suggested that this is what occurs during prolonged hemorrhagic hypotension. The hypothesis supposes that although glomerular filtration virtually ceases during hemorrhagic hypotension, some blood flow persists in the medulla, though at a reduced rate. Because of reduced glomerular filtration, failure of input of osmolar constituents (largely sodium salts) to the countercurrent multiplier system, in the face of continued blood flow through the vasa recta, results in wash-out from these vessels and the surrounding interstitium. Tissue slice analysis by Boylan and Asshauer (quoted by Kramer(3)) of dog kidneys subjected to shock states appears to support this hypothesis.

The purpose of the present investigation was to examine the possible existence of such a wash-out phenomenon by employment of conventional clearance methods, with simultaneous measurement of arterial and renal venous concentrations of total osmolality and sodium.

Methods. Experiments were done in 10 dogs averaging 21 kg BW. Under pentobarbital anesthesia, a right flank approach was made to the kidneys. This permitted passage of a polyethylene catheter into the right renal vein from the abdominal vena cava, following introduction *via* the left femoral vein. Both ureters were catheterized.

Clearance measurements included PAH and creatinine, sodium, and osmolarity. Standard chemical procedures were used for PAH and creatinine analysis(4,5). Osmolar concentrations in plasma and urine were determined with a Fiske freezing point depression apparatus, and sodium with a Coleman flame photometer.

To induce an adequate diuresis, and to provide maximal engagement of the countercurrent mechanism, 2.5% NaCl was continuously infused at a rate of 4 ml/min. Urine periods averaged 10 to 15 minutes in duration, depending on rate of urine production. However, when urine flow became scanty after the first third of the hypotensive period, further collection was ordinarily not attempted during the latter two-thirds of oligemia.

The hemorrhagic shock procedure was to bleed to 60 mm Hg arterial pressure for 90 minutes, then to 40 mm Hg for 45 additional minutes, at which time all blood was restored.

Results. 1. PAH and creatinine clearance. The average trends of 10 experiments with S.E. appear in Fig. 1, related to bleeding volume and mean arterial blood pressure. Values are for both kidneys in all cases. Changes are related to the per cent of hypotension and post-transfusion. The latter averaged 314 minutes (range 235-355).

The trends are in conformity with previous

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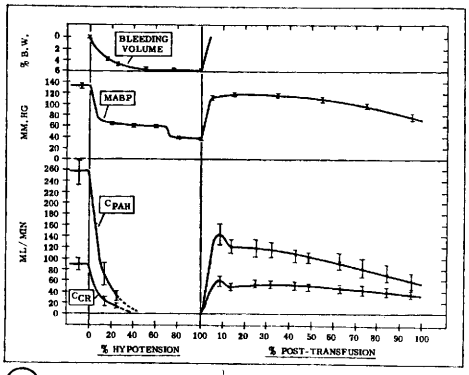
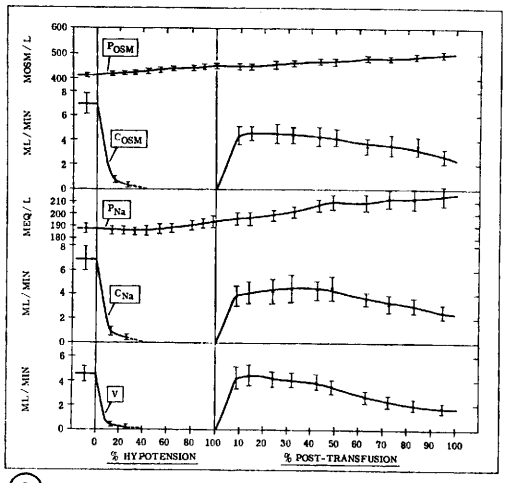


(1)



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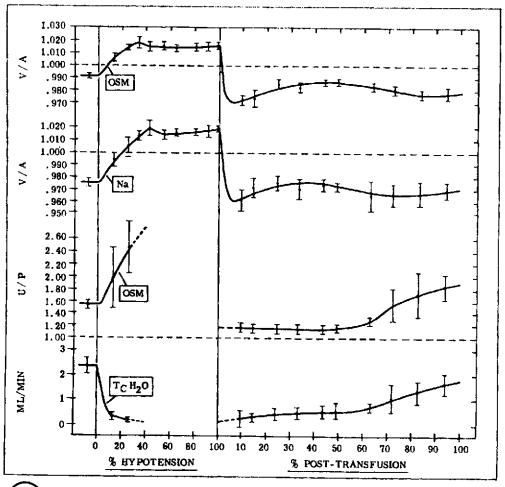

(3)

FIG. 1. Mean trends of clearance of creatinine (C_{CR}) and PAH (C_{PAH}) during oligemic and normovolemic phases of hemorrhagic shock. Data in this and subsequent figures are for both kidneys. MABP: Mean arterial blood pressure. Vertical lines in this and subsequent figures are plus or minus one standard error of mean. Dashed lines in curves of C_{CR} and C_{PAH}, during hypotension, are tentative extrapolations of trends beyond the limit of adequate urine collection.

FIG. 2. Osmolar (C_{Osm}) and sodium clearance (C_{Na}) during hemorrhagic shock, with related changes in urine volume, V.

FIG. 3. Renal venous over arterial concentration ratios for osmolality and sodium during hypotension and post-transfusion, as related to changes in urinary concentrating ability. The latter is examined by the alteration in U/P of osmolality, and volume of solute-free water absorbed by the kidneys, $T_{c_{H_2O}}$.

findings(6,7), manifesting sharp decreases in C_{PAH} and C_{CR} following hemorrhage. Upon transfusion, C_{CR} was restored to about two-thirds of control, but C_{PAH} to only about half.

2. *Osmolar and sodium clearance and urine volume.* Fig. 2 shows the alterations in C_{Osm} and C_{Na} during the phases of hypotension and post-transfusion, as related to gradual increase in plasma osmolality and sodium concentration. The alterations in these functions are rather directly dominated by the alterations in glomerular filtration rate (C_{CR}), in turn largely determined by effective plasma flow (C_{PAH}). As anticipated, changes in C_{Osm} and C_{Na} are quite similar.

Oliguria is the consequence of the marked decrement in GFR following hemorrhage. It should be noted that urine volume (V) returns approximately to the control value following transfusion, while C_{Osm} and C_{Na} restore to only two-thirds.

3. *Relation of V/A of total osmolality and sodium to alteration of concentrating power of the kidney.* Renal vein plasma osmolality increases to a range of 1.015-1.020 above that in the arterial plasma during hemorrhagic hypotension (Fig. 3). Since urinary excretion virtually ceases, the higher venous concentration signifies renal wash-out. Sodium shows a similar trend.

Upon transfusion, V/A osmolality showed phases of decrease below the control average. This could signify replenishment of osmolar constituents lost during hypotension. Sodium showed parallel trends. The average U/P of osmolality showed an increase early in hypotension, as urine volume was reduced.

The large SE's of this function at 14 and 24% of the period of hypotension indicate considerable variability of the initial effects of hemorrhage. Thus, although 7 of the experiments showed initial increases in osmolar U/P, the remaining 3 manifested an early decline in the ratio. However, as wash-out continued, the concentrating power was markedly reduced, as evidenced by the low U/P values observed during the first half of the post-transfusion period. During this time, U/P Osm averaged 1.16 compared to the control average of 1.55. The lowered ratio was observed at urine volumes comparable to control.

Another index of tubular concentrating power is $T_{c_{H_2O}}$. This is calculated as the difference between urine volume (V) and the osmolar clearance:

$$C_{H_2O} = V - C_{Osm}$$

When C_{H_2O} is negative, this signifies water reabsorption in excess of solute, and this moiety becomes $T_{c_{H_2O}}$. Fig. 3 shows marked reduction in this parameter during hypotension, with persistance of reduction until 60% of the post-transfusion period has elapsed, after which it slowly improves. The seeming paradox of increase in U/P Osm as $T_{c_{H_2O}}$ decreases early in hypotension simply reflects the fact that, although impairment of concentrating power is manifested by absolute decrease in $T_{c_{H_2O}}$, nevertheless reabsorption of the markedly reduced filtered load of water is still somewhat in excess of total solute reabsorption, accounting for some initial increase in U/P in most experiments.

Discussion. The data presented support the concept of a wash-out of the osmolar constituents of the kidney as an explanation of the loss of concentrating power in hemorrhagic shock. Unfortunately, the unreliability of C_{PAH} as an index of true plasma flow in the shock kidney(6,7) has prevented a quantitative measurement of the rate of turnover of osmolarity, including sodium, in the present series. However, interesting speculation is made possible by using values for direct plasma flow obtained in an earlier series of experiments done in a similar fashion(7). In the latter series, plasma flow averaged 0.6 ml/min/g kidney weight during the entire hypotensive period.

Arterial plasma osmolality averaged 433.3 Mosm/liter and venous plasma osmolality 439.2, in the present series during hypotension. Since V/A averaged 1.0136, this meant the addition of 5.9 Mosm/liter of renal venous plasma flow (439.2-433.3). Total plasma flow per g kidney weight for the 150 minutes of hypotension is taken as 90 ml (150 $\times$ 0.6 ml/min/g). For purposes of permitting conventional calculations, this equals 90 liters/kg of kidney weight (90 $\times$ 1000), and is equivalent to total removal of 530 Mosm/kg kidney weight (5.9 $\times$ 90). Accepting a figure of 80% for total kidney tissue water(8), this equals 660 Mosm/kg of kidney tissue water $\left(\frac{530}{800} \times 1000\right)$ or 4.40 (660/150) Mosm removed per min per kilogram of kidney tissue water.

Since this represents an operation tending to reduce kidney osmolality to isosmotic proportions (*i.e.*, the calculated removal represents an amount in excess of the value (433.3) taken as isosmolality during salt infusion), such calculation strongly supports the evidence for removal of osmotic constituents from a highly hyperosmotic zone. For comparison, Boylan and Asshauer have found osmolalities of dog kidney slices ranging from 520 to over 900 Mosm/kg tissue water in progression from tissue of the outer medulla to the papillary tip, and in which the value for the cortex was *ca.* 320 Mosm/kg. Values would be expected to be higher in our series because of salt-loading.

A similar calculation for sodium removal gives a figure of 244 meq/kg of kidney tissue water, compared with the expected isosmotic value of 188 in the present series. The slice method for comparable values of sodium in control dog kidney slices showed 161 meq/kg tissue water in the outer medulla as compared to 289 in the papilla(9). The average value for cortex was 77 meq/kg tissue water. These values were for animals not subjected to salt loads, and would be expected therefore to be lower than in the present series.

Since sodium concentration is low in the

intracellular phase of most tissue cells, a wash-out of an extracellular pool of hyperosmotic sodium concentration appears indicated, *viz.*, from the vasa recta and adjoining medullary interstitial spaces. However, this could be supplemented by more complete removal of intraluminal sodium, and perhaps more complete removal of sodium in transit through those cells of the nephron active in sodium reabsorption. However, except in the loop of Henle, this should not be greatly in excess of that in the arterial plasma.

In the absence of quantitative data on renal plasma flow, further speculation on the mechanism of wash-out is unwarranted. For this reason also, no attempt has been made to calculate the rate of restoration of osmolality during the post-transfusion recovery period, where errors would be greater because of the greater volume of plasma flow. It is of considerable interest that the kidneys in the present series showed signs of recovery of concentrating power even as the animals as a whole often gave indication of passing into irreversible shock.

Summary. The influence of hemorrhagic shock on renal clearance of PAH, creatinine, osmolar constituents, and sodium was examined in relation to changes in the kidney's ability to concentrate urine. By comparison of renal venous and arterial concentrations of osmolality and sodium, and relating these to changes in C_{CR}, C_{PAH}, and urine volume, evidence was supplied which appeared to support the hypothesis that the loss of concentrating power was ascribable to wash-out of the papillary zone of hyperosmolarity.

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Effect of Hypercholesterolemia on Digoxin Tolerance. (27874)

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The effect of a marked elevation of serum cholesterol on digitalis tolerance was determined by performing digitalis bioassays in normocholesterolemic and hypercholesterolemic male rabbits.

Method and materials. The control animals consisted of 21 male adult New Zealand albino rabbits, average weight 3048 g (range 2607-3647). Seventeen male rabbits of similar age, breed, nutrition and weight (average 3127 g with a range of 2840-3820) composed the hypercholesterolemic group. Hypercholesterolemia was produced by feeding a diet containing 1% cholesterol for from one to 8 weeks. This diet was prepared by mixing 10 g of cholesterol dissolved in 50 g soy bean oil with 1,000 g Purina rabbit pellets.

Sodium pentobarbital (Nembutal), 65 mg was injected intraperitoneally and was followed in 10 minutes by light ether anesthesia. Blood was obtained for cholesterol(1) and potassium(2) determinations. Digoxin,*

* Lanoxin, Burroughs Wellcome & Co., Tuckahoe, N. Y.